ORIGINAL RESEARCH

# Breast cancer associated with primary hyperparathyroidism: a nested case control study

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**Background:** Primary hyperparathyroidism (pHPT) is associated with an increased risk of developing breast cancer, but little is known about the underlying factors. The aim of this study was to compare women with a history of pHPT and a reference population in terms of standard factors predictive of prognosis and response to therapy for breast cancer.

**Methods:** We analyzed data collected from the National Swedish Cancer Register and from two regional oncologic center registries. Seventy-one women with breast cancer and a history of parathyroid adenomectomy were compared with 338 matched controls with breast cancer only. Tumor size, stage, hormone receptor status, lymph node status, cause of death, and cumulative survival were analyzed.

**Results:** The mean age was $69 \pm 11$ years (95% confidence interval [CI]: 68–70) in both groups and the mean time interval between the parathyroid surgery and breast cancer diagnosis was $91 \pm 68$ months (95% CI: 72–111). There were no differences between the two groups regarding size, stage, lymph node metastases, or survival, but none of the cases with a history of pHPT were found in Stage III or IV.

**Conclusion:** In conclusion, factors predictive of prognosis and response to therapy in women with a history of pHPT and breast cancer are similar to those in breast cancer patients without pHPT.

**Keywords:** breast cancer, primary hyperparathyroidism, prognostic factors

## Introduction

Primary hyperparathyroidism (pHPT) is associated with an increased risk of premature death in malignant disorders.[1–3] The prevalence of pHPT is highest in postmenopausal women, ie, 3%–4%, and the origin is most often a single parathyroid adenoma.[4,5] Certain malignant tumors are over-represented, and breast cancer is the most frequent, comprising 25% of the malignancies diagnosed after parathyroid adenomectomy in women.[3,6] An increased frequency of parathyroid adenoma and significantly higher serum calcium and parathyroid hormone levels have been documented in patients treated for breast cancer compared with healthy controls.[7] These findings were unrelated to clinical staging or antitumor therapy. Little is known about the association between pHPT and the development of breast cancer. Causal relationships have been discussed, and various shared predisposing genetic and environmental risk factors have been hypothesized. The aim of this study was to evaluate factors predictive of prognosis and response to therapy in a cohort of breast cancer patients with a history of pHPT and to search for a potential link between pHPT and breast cancer.

## Patients and methods

We used the National Swedish Cancer Register to select the study population. It is a well-validated register, where under-reporting is 3%–4%.[8] All malignant and a few benign tumors, including parathyroid adenomas, are reported to the register by both the treating physician and the pathologist making the diagnosis. The diagnoses are coded using the International Classification of Diseases 7th revision (ICD-7). Requisites for inclusion of cases in this study were parathyroid adenomectomy of a single parathyroid adenoma (ICD-7 1951) and a subsequent diagnosis of invasive breast cancer (ICD-7 170). To minimize confounding by diagnosis, we excluded all cases with a breast cancer diagnosis before primary hyperparathyroidism (n = 59). All males were excluded, as were all women with a diagnosis of breast carcinoma in situ.

We identified 71 women with breast cancer and previous surgery for pHPT during the period from January 1, 1992 to December 31, 2006. For each patient, five control subjects with breast cancer but no history of parathyroid surgery, matched for age and time period, were enrolled. Using the national registration number, a unique identifier for each Swedish resident made linkage possible to two of Sweden's six regional breast cancer registers. The registers for the Stockholm-Gotland and Uppsala-Örebro regions cover a population of 3.9 million, or 43% of the Swedish population. Data on tumor size, stage, and hormonal receptor status were retrieved. The American Joint Committee on Cancer staging system for breast cancer was used.[9] Dates of death until December 31, 2009 and causes of death until December 31, 2008 were retrieved from the Swedish Cause of Death Register. The study was approved by the ethical committee at the Karolinska Institutet, Stockholm, Sweden.

### Statistical analysis

Statistical analysis was performed with the PASW for Windows statistical package (18.0;PASW Inc., Chicago, IL). The Student's two-tailed, unpaired *t*-test was used to compare mean tumor size between the cases and control subjects. The Chi-square test was used to compare lymph node involvement, and receptor status. The distributions of tumor characteristics of cases and controls were compared by Pearson Chi-Square test. When cells had expected counts less than 5, a corresponding exact test was applied. Survival time was calculated as the number of months between the date of diagnosis and date of death, or date at end of follow-up (whichever occurred first). Breast cancer survival is presented in a Kaplan–Meier plot and tested with the logrank test. $P < 0.05$ was considered to be statistically significant.

## Results

The mean age at diagnosis of breast cancer was 69 years, with a standard deviation (SD) of 11 years (95% confidence interval [CI]: 68–70) in both groups. The age distribution for the cases and controls is presented in Table 1. The interval between the parathyroid adenoma operation and breast cancer registration ranged from 1 to 292 months (mean 91 months, SD 68 months, 95% CI: 72–111). Tumor size, stage, axillary lymph node status, and hormone receptor status are presented in Table 2. None of the prognostic factors analyzed in this study differed between the women with and those without a history of pHPT. The duration of follow-up ranged from 0 to 307 months (mean 80 months, SD 59 months, 95% CI: 74–86). In December 31, 2009, 29 (41%) cases and 150 (44%) controls had died. There was no statistically significant difference between the two groups in cumulative breast cancer-specific survival (see Figure 1).

## Discussion

The mechanisms underlying the coexistence of pHPT and certain malignancies, including breast cancer, are still unknown. To our knowledge, the prognosis of breast cancer in women with a history of pHPT has not been studied systematically. The aim of our study was to investigate whether the prognosis for breast cancer associated with pHPT differs from that for breast cancer in the background population. Comparing tumor size, stage, hormone receptor status, and the most important prognostic factor, axillary lymph node status, we found no difference between women with and those without a history of pHPT. Remarkably, none of the cases had Stage III or IV disease. Breast cancer-specific survival was the same in the two groups.

Our study design has some limitations. Data on the prognostic factor, and predictive factor for trastuzumab therapy,

**Table 1** Age distribution of women with primary hyper-parathyroidism and breast cancer (cases) and women with breast cancer only (controls)

| Age group (years) | Cases (n = 71) | Controls (n = 338) |
|---|---|---|
| | (n) | (n) |
| 0–49 | 2 | 10 |
| 50–54 | 5 | 24 |
| 55–59 | 8 | 34 |
| 60–64 | 9 | 43 |
| 65–69 | 11 | 54 |
| 70–74 | 9 | 41 |
| 75–79 | 16 | 77 |
| 80+ | 11 | 55 |

**Note:** Mean age at breast cancer diagnosis (year ± standard deviation) 69 ± 11, 95% confidence interval 68–70.
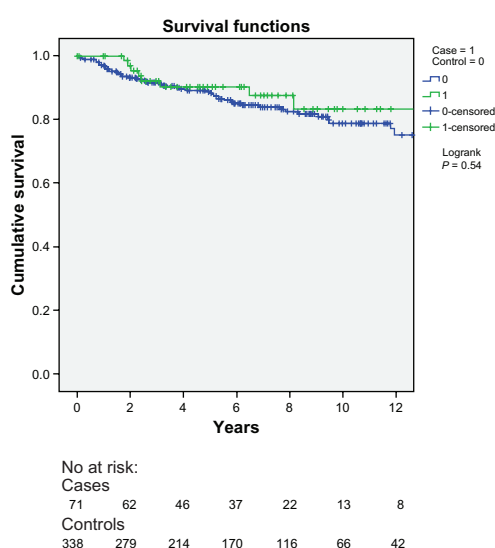
**Table 2** Tumor characteristics in women with pHPT+breast cancer (cases) and women with breast cancer only (controls)

| | Cases (n = 71) | Controls (n = 338) | P-value |
|---|---|---|---|
| **Tumor size (mm ± SD)** | 18 ± 10 | 20 ± 14 | 0.27 |
| Missing | 4 | 29 | |
| **Axillary lymph node status** | | | |
| Negative | 35 (59%) | 176 (65%) | |
| 1–3 positive nodes | 11 (19%) | 63 (23%) | |
| ≥4 positive nodes | 13 (22%) | 32 (12%) | 0.11 |
| *Missing* | *12 (17%)* | *67 (20%)* | |
| **Tumor stage** | | | |
| I (T1 + N0) | 29 (46%) | 149 (51%) | |
| IIa (T1 + N1 or T2 + N0) | 25 (40%) | 77 (27%) | |
| IIb (T2 + N1 or T3 + N0) | 9 (14%) | 49 (17%) | |
| III (T3 + N1 or T4) | 0 (0%) | 4 (1%) | |
| IV (M1) | 0 (0%) | 11 (4%) | 0.13[c] |
| *Undefined* | *8 (11%)* | *48 (14%)* | |
| **Hormone receptor status** | | | |
| Positive[a] | 46 (88%) | 217 (84%) | |
| Negative[b] | 6 (12%) | 42 (16%) | 0.38 |
| *Missing* | *19 (27%)* | *79 (23%)* | |

**Notes:** [a]ER-positive, P-positive or -negative according to local laboratory and clinical standards. [b]ER- and PR-negative. [c]Exact Pearson Chi-Square test

HER-2/neu, were incomplete, and there were no data on the cell proliferation marker, Ki-67. Elston–Ellis tumor grade could not be properly analyzed due to too many missing data, particularly in the earlier periods when the grade was not registered prospectively. Risk factors for breast cancer and data on calcium and vitamin D levels were not available in the registries.

We cannot exclude the presence of pHPT in the control group but, because the prevalence of pHPT in the population is low, it may affect only isolated cases.[5]



**Figure 1** Kaplan–Meier plots of breast cancer-specific survival in women with pHPT + breast cancer (cases) and women with breast cancer only (controls).

Our study design does not allow for comparisons between different treatment modalities, because the registry does not contain such data. However, the bias induced by differences in treatment strategy is likely to have been negligible, because there was near to complete compliance with regional/national treatment guidelines, and also by matching of five controls per case from the same region.

The strengths of the study are that the registers used are well validated and that two important prognostic factors, ie, tumor size and lymphatic involvement, were included.[8,9] The risk of confounding by diagnosis was minimized by excluding all cases with a breast cancer diagnosis before the diagnosis of pHPT.

The coexistence of pHPT and breast cancer, recognized in several case reports and confirmed in large population studies, has given rise to much speculation concerning possible etiologic links.[1,3,6,7] It remains to be elucidated whether the association between pHPT and breast cancer is due to predisposing genetic or environmental risk factors. Abnormalities in calcium metabolism have been associated with breast cancer risk, but the results reported from different studies have not been consistent. Although higher serum calcium levels have been reported from breast cancer cohorts, no correlation was found between calcium level and tumor stage.[7,10,11] A causal relationship between hypercalcemia and malignancy seems unlikely, given that the risk of breast cancer remains unchanged at least 15 years after parathyroid adenomectomy.[3] Vitamin D may be a key factor, and there is evidence of potential links between vitamin D deficiency and the development and prognosis of breast cancer, as well as aggravated clinical presentation of pHPT and increased parathyroid tumor growth.[12–16] A modestly reduced incidence of breast cancer associated with a higher intake of vitamin D was reported from a meta-analysis of observational studies.[17] The results from a randomized clinical trial of calcium and vitamin D supplementation versus placebo among postmenopausal women for a mean of seven years showed no detectable effect on breast cancer risk.[18] However, the supplementation dose was rather low (1000 mg of elemental calcium with 400 IU vitamin $D_3$ daily), additional use of calcium and vitamin D supplements was allowed, and the discontinuation rate was quite high. Comparing data on vitamin D levels from different observational studies is complicated by differences in definitions and diagnostic methods.[19] Furthermore, many factors may interfere with the interpretation of vitamin D status, such as age, body mass index, liver and kidney function, chronic illness, and sun exposure.[19,20] Overweight is another reported risk factor that has been coupled with increased risk of postmenopausal breast cancer, pHPT, and vitamin D deficiency.[11,21–23]

There has also been speculation about other factors, such as genetic predisposition, that may influence vitamin D levels. Familial accumulation of hyperparathyroidism and breast cancer, as well as isolated cases with high penetrance cancer susceptibility genes, have been reported.[24,25] Hitherto, exposure to ionizing radiation is the only established risk factor with a confirmed dose-response relationship for both parathyroid adenoma and breast cancer.[26,27]

## Conclusion

In this study, women diagnosed with breast cancer and having an earlier history of pHPT had the same tumor risk factors and the same breast cancer-specific survival as women with breast cancer and no previous history of hyperparathyroidism.

## Acknowledgments

## Disclosure

The authors report no conflicts of interest in this work.

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